Impact of Real-Time Therapeutic Drug Monitoring on the Prescription of Antibiotics in Burn Patients Requiring Admission to the Intensive Care Unit

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ABSTRACT

Background: As pharmacokinetics after burn trauma are difficult to predict, we conducted a 3-year prospective, monocentric, randomized controlled trial to determine the extent of under and overdosing of antibiotics and further evaluate the impact of systematic therapeutic drug monitoring (TDM) with same day real-time dose adaptation to reach and maintain antibiotic concentrations within therapeutic range.

Methods: Forty-five consecutive burn patients treated with antibiotics were prospectively screened. Forty fulfilled inclusion criteria; after one refusal and one withdraw consent, 19 were randomly assigned to an intervention group (real-time antibiotic concentration determination and subsequent adaptations), and 19 to a standard-of-care group (antibiotic administration at physician's discretion without real-time TDM).

Results: Seventy-three infectious episodes were analyzed. Before intervention, only 46/82 (56%) initial trough concentrations fell within the range. There was no difference between groups in initial trough concentrations (adjusted HR=1.39 [95%CI: 0.81-2.39], p=0.227) or time to reach the target. However, thanks to real-time dose adjustments, trough concentrations of the intervention group remained more within the predefined range (57/77 [74.0%] vs. 48/85 [56.5%], adjusted OR=2.34 [95%CI: 1.17-4.81], p=0.018); more days were spent within the target range (193 days / 297 days on antibiotics [65.0%] vs. 171/311 [55.0%], adjusted OR=1.64 [95%CI: 1.16-2.32], p=0.005); and fewer results were below target trough concentrations (25/118 [21.2%] vs. 44/126 [34.9%], adjusted OR=0.47 [95%CI: 0.26-0.87], p=0.015). No difference in infection outcomes was observed between study groups.

Conclusions*:* Systematic TDM with same day real-time dose adaptation was effective in reaching and maintaining therapeutic antibiotic concentrations in infected burn patients, which prevented both over- and under-dosing. A larger multicentric study is needed to further evaluate the impact of this strategy on infection outcomes and the emergence of antibiotic resistance during long-term burn treatment.

This study was registered with the ClinicalTrials.gov platform on September 27th 2013.
Trial Registration: NCT01965340.

Keywords: pharmacokinetics of antibiotics, burn patients, therapeutic drug monitoring

INTRODUCTION

Sepsis is a major cause of morbidity and mortality among burn patients (1-4). Burn patients often suffer from recurrent infections that are difficult to treat, caused by nosocomial multidrug-resistant microorganisms (5, 6) . The rapid spread of antibiotic resistance is currently a major challenge in burn care. As the number of new anti-infective drugs entering the market is disappointingly low, strategies to preserve the efficacy of currently approved antibiotics are urgently needed (7, 8).

Antibiotic stewardship programs may reduce the selective pressure induced by antibiotic misuse (9). In addition to rapidly identifying bacterial infections, systematically de-escalating, and shortening the duration of antibiotic treatment, these bundles also include the close monitoring of pharmacokinetic-pharmacodynamic (PK-PD) characteristics to further optimize antibiotic treatments while decreasing the risk that resistance will develop (10).

Therapeutic drug monitoring (TDM) was introduced into clinical practice primarily to improve efficacy and to limit the toxicity of antibiotics with narrow therapeutic windows (e.g., vancomycin, aminoglycosides). However, with the increasing availability of rapid-dosing techniques, the number of drugs that can be measured in the plasma of patients has grown tremendously over the last decade (11). It is currently possible to monitor blood concentrations of antibiotics in real-time to improve efficacy and avoid under-dosing, which can favor bacterial regrowth and the emergence of resistant organisms. Several studies have demonstrated that TDM improves the prescription of antibiotics in various populations of hospitalized patients, including critically ill patients, with a direct impact on outcomes (11-17).

Altered metabolism, dramatic fluctuations in drug clearance and rapid modifications in the volume of distribution make the administration of antibiotics to burn patients particularly complex. However, no recommendations exist to specifically guide antibiotic dosage after

burn trauma and only few studies have prospectively and systematically explored antibiotic PK in such conditions. Recently, we demonstrated that burn patients very often require drastic modifications of the standard antibiotic doses recommended by the manufacturers to avoid both under- and over-dosing (15). We conducted a 3-year prospective, monocentric, randomized, controlled clinical trial to determine the extent of under and overdosing of antibiotics and further evaluate the impact of systematic TDM with same day real-time dose adaptation to reach and maintain antibiotic concentrations within therapeutic range.

MATERIALS AND METHODS

Study design and setting

This prospective, monocentric, randomized, controlled trial was conducted between October 2013 and October 2016 at the Lausanne Burn Intensive Care Unit (BICU), a five-bed Swiss tertiary reference BICU nested in the 35-bed medico-surgical ICU of the Centre Hospitalier Universitaire Vaudois (CHUV).

Ethics

This study was approved by the *Commission cantonale d'éthique de la recherche sur l'être humain* (#195/13) and performed in accordance with the Declaration of Helsinki and its later amendments. It was registered with the https://clinicaltrials.gov/ platform (NCT01965340) and adherence to good clinical practice and study protocol was regularly monitored by the Lausanne Clinical Trial Unit. Written informed consent was obtained from all participants or proxies at the time of enrollment.

Selection Criteria

All patients admitted to the BICU after burn trauma and receiving intravenous antibiotics were prospectively screened for inclusion. Patients younger than 14 yr, those who refused informed consent, those with length of hospital stay <72 hr, and those who were legally incompetent were excluded (**Figure 1**).

Data collection

Patient age, sex, glomerular filtration rate (calculated using the Cockcroft-Gault formula) and burn severity scores (total body surface area [TBSA] affected, presence of burn inhalation injury (18, 19), Ryan score, and Simplified Acute Physiology Score [SAPS II]) were collected

prospectively. All infection episodes corresponding to a monitored antibiotic course were characterized, as previously described [see supplemental information in (15)]. Concomitant sites of infection, including sites of primary bloodstream infections, were considered as separate episodes. Episodes of infection caused by several microorganisms were considered only once. To guide the pharmacologic recommendation a minimum inhibitory concentration (MIC) was determined for the causative organism whenever possible.

Antimicrobial treatment

Information on the date and time of antibiotic administration, dosage and duration of treatment were prospectively collected from the clinical information system (Metavision®; IMDsoft, Tel Aviv, Israel). Total antibiotic consumption was reported as defined daily dose (DDD) (http://www.whocc.no/atc_ddd_index/)(20). Antibiotics were started according to the manufacturer's recommendations, with modifications for the calculation of glomerular filtration rate when appropriate (See **Supplemental Material file S2**). From October 2013 until July 2015, all antibiotics were given via 30-minute infusion. In August 2015, the duration of infusion time of β-lactams was increased to 2 hours, starting from the second dose due to an update of local protocols regarding all critically ill patients, including burn patients, receiving β-lactams. Because systematic TDM of aminoglycosides and vancomycin are part of the standard of care at our institution, those treatment courses were not included.

Intervention

After informed consent was obtained, patients were randomized to an *intervention group* (patients with real-time TDM and online antibiotic adaptation) or to a *standard-of-care group* (patients for whom antibiotic concentrations would be determined only after completion of the study). Randomization was stratified according to burn severity (TBSA <20%, 20–40%,

41–60%, >60%) (**Figure 1** and **supplemental Figure S1**). All infectious episodes and antibiotic courses during a given patient's stay were handled according to the initial randomization result. Blood was drawn from each patient every other day (QOD) for TDM until the end of the antibiotic course, but antibiotic concentrations were determined in real-time only for patients randomized to the intervention group, for whom the prescription of antibiotics was further adapted the same day according to a standardized adaptation protocol by dedicated independent pharmacologists and infectious disease specialists to meet predefined pharmacodynamic targets (see **Supplementary Material adaptation protocol file S1**). An every other day TDM regimen was chosen in order to rapidly adjust the antibiotic doses while taking into account the time needed for β-lactams to reach the steady state after dose adaptation. In the standard-of-care group, the prescription of antibiotics was modified at the clinician's discretion. Upon clinician's special request, rescue TDM could however be determined in real-time for any patient randomized to the standard-of-care group.

Evaluation of trough antibiotic concentrations

Antibiotic serum levels were determined (2.7 ml blood samples) by the Laboratory of the Service of Biomedicine at CHUV using a multiplex assay with high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) according to previously published validated analytical methods with lower limits of quantification of 0.02-0.5 mg/L (21, 22). The median total amount of blood withdrawn from each patient reached 13.5 ml [8.1; 25.0].

Total drugs levels were measured, but estimated unbound concentrations were calculated using available data for protein binding (see our local adaptation protocol file in **Supplementary Material S1**). Antibiotic serum levels were obtained within 6 hours on the day of the request from Monday to Friday and subsequent adaptation of antibiotic prescription

was performed the same day. On the weekend, blood samples were analyzed and available on Monday afternoon where the adaptation took place. The empirical dosages used at initiation of antibiotic therapy are presented in **Supplementary Material S2.** Trough serum concentrations of antibiotic had to exceed the MIC of the causative microorganism(s). If the MIC was not available (e.g. the infection was not microbiologically documented), the MIC_{90} (according to the European Committee on Antimicrobial Susceptibility Testing database) of the most frequently occurring Gram-positive and Gram-negative bacteria isolated at our burn ICU was determined (15, 23) (see **Supplemental Material adaptation protocol file S1**). The upper limits of trough concentrations were also specified in the adaptation protocol file.

Doses adaptations were performed using pre-defined "steps". The algorithm is presented in **Supplemental Material S1**. Briefly, the prescription of the given antibiotic was reduced of one step in case of excessive trough levels < 150% of the upper limit, respectively increase of one step in case of trough levels ranging between 50-100% of the minimal target. Increase/decrease of two steps was apply in case of trough levels exceeding 150-200% of the upper limit, respectively ranging between10-50% of minimal target.

Outcomes

The first predefined primary pharmacokinetic outcomes were the time required to achieve anti-infective serum concentrations within the predefined target range and the proportion of trough antibiotic serum concentration measurements that fell within the target range during a single course of treatment with a given anti-infective agent. Secondary predefined endpoints included total antibiotic consumption as expressed in DDD, clinical resolution of infectious episodes and proportion of antibiotic concentration measurements above and below predefined targets.

Sample size

We assumed that 50% of patients would remain in the predefined target range without TDM intervention and that trough concentration measurements would increase this result to 80%. Therefore, we calculated that the study would need to include a sample of 90 patients assuming each patient had only one episode of infection and one antibiotic cure (α [two-sided]=0.05, β=0.8).

Statistical analysis

Continuous normally and non-normally distributed variables are reported as means ± standard deviations and medians with interquartile ranges (p25; p75), respectively. Categorical variables are reported as frequencies and percentages. An intention-to-treat analysis of all randomized patients was performed for all endpoints. Per-protocol analysis was performed for the main outcomes, excluding unblindings for rescue TDM requests in the standard-of-care group. All analyses were adjusted for burn severity (stratified randomization). Results of unadjusted analyses are also presented. As there were very few patients with TBSA>60% we used 3 levels of burn severity for the analysis: TBSA<20%, 20%-40% and >40%. Difference between groups regarding time to achieve anti-infective concentrations within the predefined target range was assessed using Cox proportional hazards model. Effect of the intervention on the proportion of antibiotic concentration measurements that fell within the target was evaluated with a logistic regression model. To assess the effect of systematic TDM with same day real-time dose adaptation on the frequency of antibiotic concentrations remaining within the predefined target range, we first compared the initial concentrations between groups, before analyzing the impact of intervention on subsequent antibiotic concentration measurements in each randomization group. Difference between groups in terms of proportions of antibiotic concentration measurements above the upper limit or below the

lower limit and proportion of days within the predefined target was assessed using logistic regression. Analysis of total antibiotic consumption (DDD) was evaluated using robust linear regression. Significance levels were set at an α-level of 0.05. GraphPad Prism software (version 5.0d; GraphPad Company, San Diego, CA) and R (version 3.3.2) were used for statistical analysis (24).

Antimicrobial Agents and Chemotherapy

RESULTS

Patient characteristics

Between October 23, 2013 and October 31, 2016, 45 out of 83 burn patients (54.2%) admitted to the Lausanne BICU received intravenous antibiotics. Ultimately, 39 (86.7%) of these were included in the study. One patient withdrew consent after randomization, so that 19 patients were finally randomized to the intervention group and 19 to the control group (**Figure 1**). Burn patients' characteristics are presented in **Table 1**. Most of the patients were male (71.1%), with median age of 55 years [31; 71] and TBSA 20% [13; 35]. Twenty-four out of 38 (63.2%) patients suffered from inhalation injury. The median duration of hospitalization was 22.5 days [12; 42] with a minimum of 4 days and a maximum of 115 days. Two patients in the standard-of-care group died (5.3%) after decisions to withdraw therapy.

Characteristics of infectious episodes

Among 38 randomized patients, we observed 73 episodes of infection, which accounted for 1.9 infection episodes per patient and 41 antibiotic cures per randomization group (**Figure 1** and **Table 2)**. The most frequently encountered infections were pneumonia (n=42, 57.5%) and burn wound infections (n=16, 21.9%) (**Tables 2** and **3)**. There were 62 (84.9%) microbiologically documented infectious episodes, with the following bacteria isolated most frequently: *Pseudomonas aeruginosa* (n=7, 11.3%), *Staphylococcus aureus* (n=6, 9.7%), and *Streptococcus pneumoniae* (n=4, 6.5%) (**Figure 2** and **Table 2**). The antibiotics prescribed most commonly were meropenem, amoxicillin, piperacillin-tazobactam, and ceftriaxone (**Table 3**). The duration of treatment (7 days [4.5; 9]) and antibiotic consumption were similar between groups (**Table 3**).

Study endpoints

A total of 244 measurements of antibiotic concentrations were obtained during the study period: 118 in the intervention group and 126 in the standard-of-care group (**Tables 2, 3** and **Supplemental Material S3)**. The MIC of the causative organism could be set as the target for 53 out of 73 (73%) episodes of infection (**Table 2**). Before intervention, (i.e. at first measurement of each antibiotic course), only 46/82 (56%) initial trough concentrations fell within the range, without difference between groups (22/41 [53.7%] in the intervention group vs. 24/41 [58.5%] in the standard of care group) (**Table 2**). Following the intervention, the numbers of through levels within the target was higher in the intervention group when considering all subsequent measurements (57/77 [74.0 %] vs. 48/85 [56.5%] adjusted OR=2.34 [95%CI: 1.17-4.81], p=0.018, unadjusted OR=2.20 [95%CI: 1.14-4.33], p=0.021) (**Tables 2** and **3**). There was no difference between groups regarding the time to reach the target (adjusted HR=1.39 [95%CI: 0.81-2.39], p=0.227, unadjusted HR=1.29 [95%CI: 0.77-2.16], p=0.341). For 17 antibiotic cures (9 in the standard-of-care group and 8 in the intervention group) there was no other measurement after the first one due to antibiotic switches (de-escalation [n=9], escalation [n=3]), patients' transfers [n=4] or end of therapy [n=1].

Patients in the intervention group spent more days within the predefined target range than did patients in the standard-of-care group (193 out of 297 days on antibiotic [65.0%] vs. 171 out of 311 days on antibiotic [55.0%], adjusted OR=1.64 [95%CI: 1.16-2.32], p=0.005, unadjusted OR=1.52 [95%CI: 1.10-2.11], p=0.012). The number of measurements below the lower limit was significantly higher among standard-of-care patients (25/118 [21.2%] vs. 44/126 [34.9%], adjusted OR=0.47 [95%CI: 0.26-0.87], p=0.015, unadjusted OR=0.50 [95%CI: 0.28-0.88], p=0.018)(**Tables 2** and **3**) while the number of antibiotic concentrations measurements above the upper limit was similar between groups (13/118 [11.0%] vs. 10/126

[7.9%], adjusted OR=1.48 [95%CI: 0.60-3.74], p=0.399, unadjusted OR=1.44 [95%CI: 0.61-3.50], p=0.412)(**Tables 2** and **3**). Young severely burn patients, especially when presenting with renal hyperclearance, were frequently - and sometimes repeatedly - below the therapeutic target (**Table 2**). Total antibiotic consumption (DDD) was not statistically different between groups (β adjusted=-0.34 [95%CI: -5.04-4.38], p=0.886, β unadjusted=-0.94 [95%CI: -5.45-3.56], p=0.677). No difference in infection outcomes was observed (33 successful episodes / 36 episodes of infection [91.7%] in the intervention group vs. 30 successful episodes / 31 episodes of infection [96.8%] in the standard-of-care group).

Rescue TDM

In the standard-of-care group, 6 measurements of trough levels necessitated rescue in 3 patients with severe burns (TBSA ≥60%; meropenem [n=3], ertapenem [n=1], piperacillin/tazobactam [n=2]). Two trough-level measurements were below the target range, and both resulted in prescription changes: one increase in drug dosage and one antibiotic switch (see **Supplemental Material S4** for more details). After removing the 3 patients for whom rescue TDM was requested from the analysis, intervention: (i) increased the frequency of trough level measurements within the predefined target range (57/77 [74.0%] vs. 35/68 [51.5%], adjusted OR=2.69 [95%CI: 1.32-5.57], p=0.007, unadjusted OR=2.69 [95%CI: 1.35-5.46], p=0.005), (ii) did not reduce the time needed to reach the target (adjusted HR=1.41 [95%CI: 0.81-2.44], p=0.225, unadjusted HR=1.32 [95%CI: 0.77-2.25], p=0.313).

DISCUSSION

This 3-year prospective monocentric, randomized controlled trial demonstrated that real-time TDM with same day dose adaptation was effective in reaching, maintaining therapeutic trough levels and avoiding underdosing in infected burn patients. At initiation of antibiotic therapy, less than 60% of patients had an adequate antibiotic trough level. However, burn patients that benefited from the intervention subsequently spent more days within the predefined target range than did patients treated with the standard-of-care. This effect held true regardless of burn severity.

To our knowledge, this is the first randomized prospective study showing that a pharmacokinetic intervention guided on real-time TDM in patients with severe burns requiring admission to the ICU effectively improves the probability of being within therapeutic range during antibiotic treatment. Over a one-year period, Patel *et al.* conducted a prospective study evaluating the impact of TDM in burn patients treated with β-lactams in a ward environment (25). The authors excluded critically ill burn patients and did not stratify the randomization according to burn severity. The results of the study showed that empiric β-lactam dosing did not consistently achieve therapeutic targets and displayed significant variability in trough antibiotic concentrations after burn trauma.

Our population of burn patients requiring ICU admission was similar to those previously described by others in terms of age, inhalation injury, and burn severity (25-30). As we and others have reported, sepsis after burn trauma is typically caused by pneumonia or infections of burn wounds (31-35). Such infections are typically due to *P. aeruginosa* and *S. aureus* (7, 8). While broad-spectrum antibiotics are among those prescribed most frequently to fight infection, the use of imipenem-cilastatin in comparison to meropenem was surprisingly uncommon, probably because of the former's greater variability in trough concentration we

reported (15). Burn trauma differentially affected the pharmacokinetics of highly protein-bound antibiotics: while ceftriaxone trough concentrations were mostly within the target range, flucloxacillin trough levels often fell below the predefined target range, probably as a consequence of increased clearance in burn patients (36, 37). In one case, this effect may have been the result of a physician's underdosage (2 g 3×/day vs. standard recommended dosage of 2 g 4–6×/day).

Our study protocol allowed physicians to ask for rescue TDM in cases of poor clinical evolution. Per physician special request, 6 rescue measurements of trough concentrations were obtained for 3 severely burned patients presenting with affected TBSA ≥60%. These interventions resulted in an increased dose of antibiotics in one case and an antibiotic switch in the second case. These unblinded requests may highlight the importance of TDM in this complex population of patients and suggest that systematic TDM, still available on request for clinicians, has progressively become the standard of care at our BICU, especially after severe burn trauma. After removing these patients from subsequent analyses, per-protocol analysis confirmed the results of the intention-to-treat analysis and the effect of real-time TDM.

Our study has several strengths. First, it is a prospective and randomized study that included consecutive burn patients admitted to a tertiary hospital BICU over the course of 3 yr. Second, our study benefited from an experienced team of certified pharmacologists and infectious disease specialists who have pioneered the analysis and interpretation of antibiotic concentrations (15, 38, 39). Third, many different infections have been documented and analyzed during this 3-year study period. Fourth, despite the evolution of clinical practice over the 3-yr study period in ways that may have lowered the full effects and benefits of TDM (e.g., the introduction of an increased perfusion duration for β-lactam maintenance doses as

356 standard of care for all critically ill patients under β-lactams at our institution), the results of
357 this study demonstrate a significant impact of real-time TDM with online antibiotic dose
358 adaptation on the prescription of antibiotics to burn patients.
359
360 This study also has some limitations. First, it was monocentric. Second, we observed a
361 decrease in the number of admissions since 2013, which explains why the number of
362 infectious episodes was lower than expected (15). Third, if MIC could be obtained for most of
363 the documented infections, it was available at time of time adaptation only in few cases.
364 Fourth, as we performed trough levels and not in the mid-interval trough levels, time above
365 MIC could not be estimated. Finally, because we randomized patients rather than infectious
366 episodes to facilitate the acquisition of informed consent, we observed a slight imbalance
367 between groups in the number of trough concentration measurements. This discrepancy may
368 also reflect the antibiotic switch (executed for de-escalation) or the longer duration of
369 antibiotic treatment in patients with drug-resistant bacteria.
370
371 In conclusion, through a 3-year prospective, monocentric, randomized, controlled trial we
372 demonstrated that systematic TDM with same day antibiotic dose adaptation is a feasible and
373 useful intervention in order to overcome pharmacokinetic variability after burn trauma,
374 thereby avoiding antibiotic under- and over-dosage. This monitoring should especially be
375 considered in the subset of patients presenting with augmented renal clearances after burn
376 trauma (40-44). TDM for most β-lactam antibiotics is now routinely available at our BICU,
377 and we further modified our internal guidelines to also perform systematic TDM in other
378 groups of ICU patients, such as those under extracorporeal membrane oxygenation support.
379 Nevertheless, further studies are needed to evaluate whether this intervention can improve
380 clinical outcome and limit the emergence of antibiotic resistance.
381

LIST OF ABBREVIATIONS

BICU	Burn Intensive Care Unit
GFR	Glomerular Filtration Rate
HPLC- MS/MS	High Performance Liquid Chromatography coupled with tandem Mass Spectrometry
ICU	Intensive Care Unit
MIC	Minimum Inhibitory Concentration
PK	Pharmacokinetic
PD	Pharmacodynamic
QOD	Every other day
TABI	Time After Burn Injury
TBSA	Total Body Surface Area
TDM	Therapeutic Drug Monitoring

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AUTHORS CONTRIBUTIONS

AF, YQ, PE, PV, AP, and FS designed the study. AF collected the data. AF, PE, YQ, JLP, PV, and EDL analyzed the data. AF, YQ, PE, OP, PV, and FS wrote the manuscript. All authors contributed to and approved the final version of the manuscript.

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573 **FIGURE LEGENDS**

574 **Figure 1:** Study flow-chart.

575 TDM: Therapeutic Drug Monitoring

576 TBSA: Total Body Surface Area

577

578 **Figure 2:** Isolated microorganisms.

579

580 **TABLE LEGENDS**

581 **Table 1**: Burn patients' characteristics.

582 **Table 2**: Characteristics of infectious episodes and antibiotic concentrations

583 **Table 3**: Study outcomes.

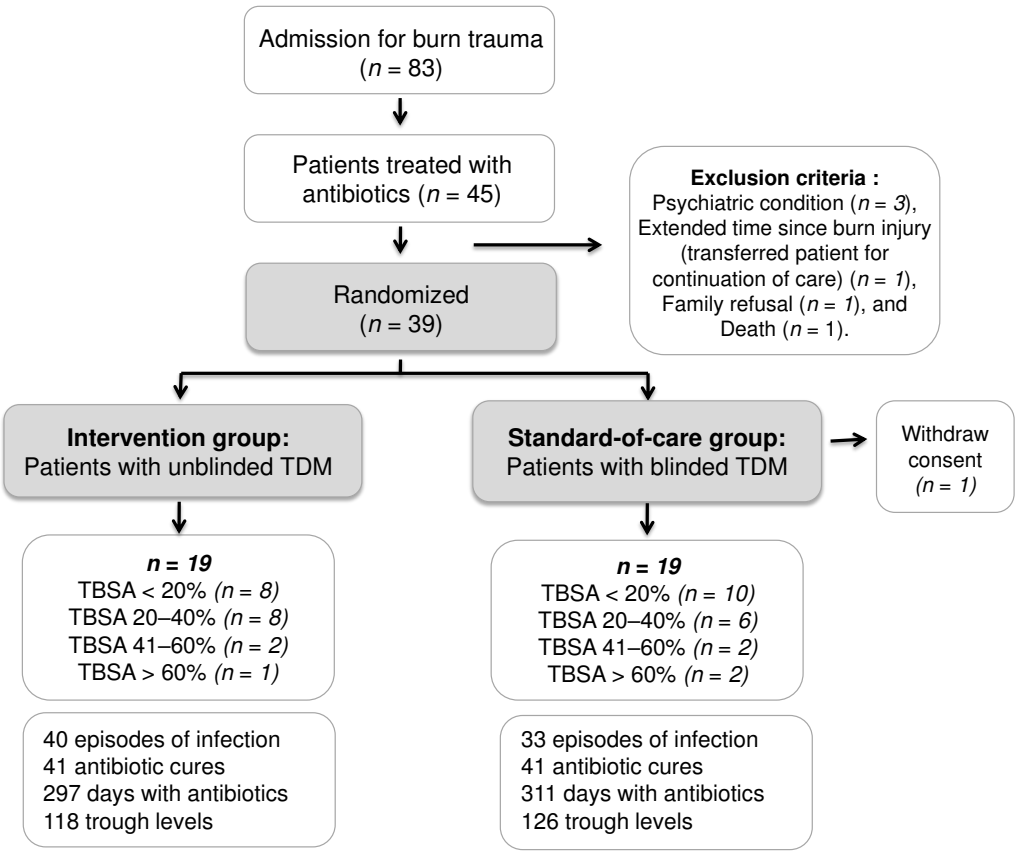

Figure 1: Study flow-chart

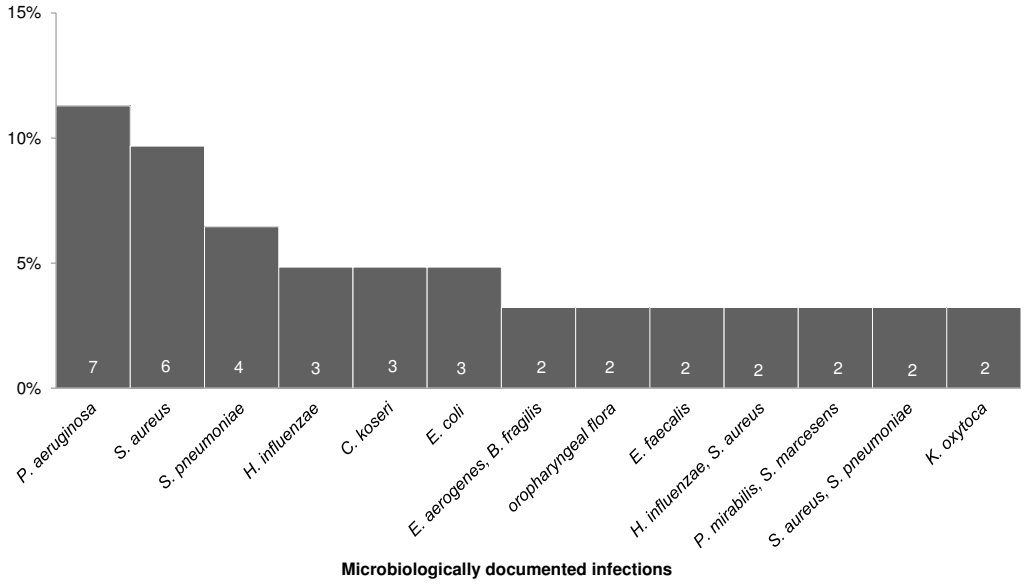

Figure 2: Isolated microorganisms

Table 1: Burn patients' characteristics

Characteristics	All patients	Patients with unblinded TDM (Intervention group)	Patients with blinded TDM (Standard-of-care group)
Number of patients (n)	38	19	19
Male, *n* (%)	27 (71.1)	15 (78.9)	12 (63.2)
Age (yrs, median [p25; p75])	55.0 [31.0; 71.3]	61.0 [32.0; 72.0]	51.0 [24.0; 69.0]
Admission weight (kg, median [p25; p75])	74.5 [67.0; 86.9]	80.0 [68.0; 95.0]	71.1 [67.0; 84.1]
TBSA affected (%) (median [p25; p75])	20.0 [12.8; 35.3]	20.0 [13.0; 25.0]	21.5 [12.0; 36.0]
< 20 (n, %)	17 (44.7)	8 (42.1)	9 (47.4)
20-40 (n, %)	13 (34.2)	8 (42.1)	6 (31.6)
41-60 (n, %)	5 (13.2)	2 (10.5)	2 (10.5)
> 60 (n, %)	3 (7.9)	1 (5.3)	2 (10.5)
SAPS II (median [p25; p75])	29.5 [21.5; 42.8]	31.0 [22.0; 42.0]	28.0 [20.0; 45.0]
Ryan score (mean ± SD)	1.2 ± 0.7	1.3 ± 0.6	1.0 ± 0.8
Inhalation lesions, *n* (%)	24 (63.2)	13 (68.4)	11 (57.9)
Length of stay (days, median [p25; p75])	22.5 [12.0; 42.0]	27.0 [13.0; 45.0]	20.0 [12.0; 40.0]
Mortality in the BICU, *n* (%)	2 (5.3)	0	2 (10)

BICU: Burn Intensive Care Unit; **SAPS II**: Simplified Acute Physiology Score II; **SD:** Standard Deviation; **TBSA** : Total Body Surface Area; **TDM**: Therapeutic Drug Monitoring.

Table 2: Characteristics of infectious episodes and antibiotic concentrations

Age (yrs)	Gender (F/M)	TBSA (%)	Episode Number	Infection types and microorganisms	Antibiotics	Day of TDM request *	Availability of MIC **	Trough level [mg/L]	Adaptation of the dosage	Free MIC [mg/L]	Total MIC [mg/L] ***
Intervention group											
19	M	41	#1	Pneumonia (*H. influenzae*)	ceftriaxone	D1	No	**40.8**	No	/	/
			#2	Burn wound *(E. coli)*	meropenem	D1	No	*8.9* ↑	Decrease	0.015	0.015
						D2	Yes	*17.7* ↑	Already adapted		
						D4	Yes	**7.7**	No		
						D6	Yes	**4.3**	No		
						D8	Yes	**6.3**	No		
						D10	Yes	*9.6* ↑	No		
89	F	20	#3	Burn wound (*S. aureus*)	cefazoline	D2	Yes	**55.1**	No	0.006	0.06
						D4	Yes	**32.3**	No		
						D6	Yes	**36.5**	Decrease [a]		
						D8	Yes	**16.7**	No		
						D10	Yes	**16.1**	No		
19	M	40	#4	Pneumonia (*S. pneumoniae*)	amoxicillin	D2	Yes	**3.3**	Increase	0.094	0.117
				Pneumonia (*S. pneumonia, S. aureus*)	amox-clav.	D4	No	**8.9**	No	0.094 / -	0.117 / -
			#5	Pneumonia (*C. koseri*)	meropenem	D2	No	**2.5**	No	0.008	0.008
						D3	No	*1.3* ↓	Increase		
						D4	Yes	**1.5**	No		
						D6	Yes	**3.7**	Increase		
						D8	Yes	*22.5* ↑	AB switch		
			#6	Sepsis	pip-tazo	D2	No	*34.2 / 4.5* ↑	No	/	/
				(non identified microorganism)		D4	No	*43.6 / 6.4* ↑	No		
						D6	No	*75.7 / 25.5* ↑	No		
						D8	No	**31.0 / 23.2**	No		

57	M	25	#7	Pneumonia *(S. aureus)*	amox-clav.	D2	No	*2.9* ↓	Increase	0.5	0.625
						D4	Yes	**4.7**	No		
						D6	Yes	**3.6**	No		
						D8	Yes	**3.8**	No		
35	F	15	#8	Pneumonia *(S. aureus)*	flucloxacillin	D5	No	*0.5* ↓	No	not in routine	not in routine
71	F	18	#9	Pneumonia (*E. aerogenes, B. fragilis*)	meropenem	D2	Yes	*10.8* ↑	Decrease	0.06 / 0.015	0.06 / 0.015
						D5	Yes	**7.9**	No		
						D6	Yes	**7.1**	No		
			#10	Peritonitis (*E. aerogenes, B. fragilis*)	meropenem	D8	Yes	**5.0**	No	0.06 / 4	0.06 / 4
						D11	Yes	**8.2**	No		
						D14	Yes	*12.1* ↑	No		
			#11	Burn wound (*E. aerogenes, S. epidermidis*)	imipenem	D2	No	**1.4 / 5.6** [b]	No	0.5 / -	0.625 / -
						D4	No	**1.9 / 7.8** [b]	No		
						D6	No	**3.1 / 12.3**	No		
						D8	No	**2.8 / 11.0**	No		
						D10	No	**2.6 / 9.7**	No		
81	M	6	#12	Pneumonia (*S. pneumoniae*)	ceftriaxone	D4	Yes	**17.2**	No	0.008	0.08
						D6	Yes	**18.4**	No		
						D8	Yes	**26.1**	No		
62	M	2	#13	Pneumonia (*E. coli, S. pneumoniae*)	ceftriaxone	D2	Yes	**23.7**	No	0.25 / 1.00	2.5 / 10.00
						D5	Yes	**33.0**	No		
66	F	20	#14	Burn wound (*P. aeruginosa*)	meropenem	D2	Yes	**1.3**	No	0.25	0.25
						D4	Yes	**0.7**	No		
						D6	Yes	**1.0**	No		
						D8	Yes	**0.7**	No		
32	M	13	#15	Pneumonia (*S. pneumoniae*)	amox-clav.	D2	Yes	**1.0**	No	0.03	0.037
					amoxicillin	D4	Yes	**0.7**	No		
						D6	Yes	**0.8**	No		
72	M	23	#16	Pneumonia (oropharyngeal flora)	amox-clav.	D2	No	*44.6* ↑	No	/	/
						D4	No	*1.3* ↓	No		
						D6	No	*1.2* ↓	No		
76	M	5	#17	Pneumonia (*K. oxytoca, S. aureus*)	pip-tazo	D5	No	*1.4 / 1.0* ↓	Increase	1.0 / -	1.54 / -
						D6	No	*3.7 / 1.3* ↓	No		
			#18	Burn wound	meropenem	D2	No	**3.6**	No	/	/

				(non identified microorganism)		D4	No	**6.5**	No		
						D6	No	**10.7**	No		
			#19	Pneumonia (*MSSA, P. mirabilis, K. pneumoniae*)	pip-tazo	D1	No	*77.7 / 15.2* ↑	AB switch	/	/
					ceftriaxone	/	No	/	/	/	/
			#20	Sepsis (non identified microorganism)	meropenem	D1	No	**10.9**	No	/	/
						D2	No	**11.7**	No		
68	M	25	#21	Pneumonia (*H. influenzae*)	meropenem	D1	No	**2.6**	No	0.25	0.25
						D2	Yes	**1.8**	No		
						D4	Yes	**1.2**	No		
					amox-clav.	D2	Yes	**13.1**	No	2.0	2.5
						D4	Yes	**8.4**	No		
						D6	Yes	**17.1**	No		
			#22	Pneumonia (*E. cloacae*)	meropenem	D2	Yes	**0.7**	No	0.03	0.03
						D3	Yes	**0.9**	No		
					ertapenem	D2	Yes	**0.3**	No	0.012	0.12
						D4	Yes	**0.3**	No		
61	M	20	#23	Pneumonia (oropharyngeal flora)	amox-clav.	D2	No	*3.1* ↓	Increase	/	
						D3	No	*2.4* ↓	AB switch		
			#24	Pneumonia (*H. alvei*)	meropenem	D1	No	**2.8**	No	0.03	0.03
						D2	Yes	**1.7**	No		
						D4	Yes	**3.3**	No		
35	M	20	#25	Burn wound (*S. bovis*)	amox-clav.	D3	No	*0.8* ↓	Increase	0.25	0.312
						D4	Yes	*2.2* [c] ↓	Increase		
						D6	Yes	*1.0* [c] ↓	No		
			#26	Pneumonia (*E. aerogenes*)	pip-tazo	D2	Yes	*0.9 / 0.2* ↓	Increase	1.5	2.31
						D4	Yes	**1.7 / 0.3** [d]	No		
						D6	Yes	*1.1 / 0.2* ↓	No		
			#27	Catheter infection (*K. pneumoniae*)	meropenem	D2	Yes	**0.3**	No	0.03	0.03
43	M	18	#28	Burn wound (*P. aeruginosa*)	pip-tazo	D2	No	*1.8 / 0.4* ↓	Increase	1.5	2.31
						D4	Yes	**29.8 / 3.4**	No		
					ceftazidime	D2	No	*7.3* [e]	No	2.0	2.5
						D4	No	*6.2* [e]	No		
31	M	48	#29, #30	Burn wound and pneumonia (*C. koseri*)	amox-clav.	D2	Yes	**5.4**	No	4.0 / 4.0	5.0 / 5.0
						D4	Yes	*3.2* ↓	No		

						D6	Yes	**7.6**	No			
					ceftriaxone	D2	Yes	**3.7**	No	0.06 / 0.032	0.6 / 0.32
			#31	Chronic pansinusitis acutised (non identified microorganism)	meropenem	D2	No	**3.2**	No	/	/
						D3	No	*1.1* ↓	Increase		
						D4	No	*0.7* ↓	Already adapted		
						D6	No	**5.7**	No		
						D8	No	**3.3**	No		
						D10	No	**7.5**	No		
						D12	No	**1.6**	No		
						D14	No	**1.8**	No		
						D16	No	**2.9**	No		
			#32	Urinary tract (*E. coli*)	ceftriaxone	D2	Yes	**8.4**	No	0.12	1.2
80	M	12	#33	Pneumonia (Enterobacteria)	amox-clav.	D2	No	*4.9* ↓	Increase	/	/
						D4	No	**11.4**	No		
						D5	No	**12.1**	No		
						D6	No	**9.7**	No		
			#34, #35	Burn wound and pneumonia (*P. aeruginosa*)	pip-tazo	D3	Yes	*3.5 / 0.9* ↓	Increase	3.0 / 6.0	4.62 / 9.24
						D4	Yes	*1.3 / 0.4* ↓	Already adapted		
						D5	Yes	**7.8 / 2.0** [d]	No		
						D6	Yes	/	/		
31	M	63	#36	Pneumonia (*S. aureus*)	ceftriaxone	D2	Yes	**18.7** [d]	No	8.0	80
						D4	Yes	**15.7** [d]	AB switch		
					amox-clav.	D2	Yes	*1.0* ↓	AB switch	1.0	1.25
					meropenem	D1	No	*0.3* ↓	Increase	0.12	0.12
						D2	Yes	**2.0**	No		
			#37	Sepsis (non identified microorganism)	meropenem	D2	No	*11.5* ↑	Decrease	/	/
			#38	Pneumonia (*S. aureus, K. pneumoniae*)	meropenem	D1	No	*10.3* ↑	Decrease	0.06 / 0.015	0.06 / 0.015
						D2	Yes	**4.0**	No		
						D4	Yes	**3.0**	No		
Standard-of-care group												
69	F	10	#39	Pneumonia (*S. pneumoniae*)	amoxicillin	D2	Yes	**4.3**	Blinded TDM	0.032	0.04
						D4	Yes	**2.8**	Blinded TDM		
						D6	Yes	**1.6**	Blinded TDM		

						D8	Yes	**1.5**	Blinded TDM		
36	M	60	#40	Pneumonia (*H. influenzae*, *E. coli*)	meropenem	D2	No	*0.8* ↓	Blinded TDM	/	/
					amox-clav.	D2	No	*2.2* ↓	Blinded TDM	1.00 / -	1.25 / -
			#41	Pneumonia (*P. aeruginosa, E. cloacae*)	meropenem	D2	Yes	/	Blinded TDM	0.12 / 0.03	0.12 / 0.03
						D4	Yes	**0.2**	Blinded TDM		
						D6	Yes	**0.5**	Blinded TDM		
						D8	Yes	**4.3**	Blinded TDM		
			#42	Ileal perforation (microoganism non identified)	meropenem	D10	No	*46.5* ↑	Blinded TDM	/	/
						D13	No	**2.3**	Blinded TDM		
						D14	No	**3.8**	No [f]		
						D16	No	*30.1* ↑	Blinded TDM		
						D18	No	*0.7* ↓	Increase [f]		
						D20	No	**2.4**	Blinded TDM		
			#43	Catheter infection (*P. aeruginosa*)	ceftazidime	D2	Yes	**8.3**	Blinded TDM	1.00	1.25
						D3	Yes	*0.5* ↓	Blinded TDM		
						D4	Yes	**6.0**	Blinded TDM		
						D6	Yes	**4.3**	Blinded TDM		
						D8	Yes	**5.0**	Blinded TDM		
			#44	Burn wound (*P. aeruginosa*)	meropenem	D2	Yes	*0.4* ↓	Blinded TDM	2.00	2.00
						D3	Yes	*0.4* ↓	Blinded TDM		
						D4	Yes	*0.5* ↓	Blinded TDM		
						D6	Yes	*1.3* ↓	Blinded TDM		
						D8	Yes	/	Blinded TDM		
						D10	Yes	**3.4**	Blinded TDM		
19	M	25	#45	Pneumonia *(S. aureus)*	meropenem	D2	No	*0.7* ↓	Blinded TDM	/	/
					flucloxacillin	D2	No	/	Blinded TDM	not in routine	not in routine
						D4	No	/	Blinded TDM		
						D6	No	*8.9* ↓	Blinded TDM		
						D8	No	*8.3* ↓	Blinded TDM		
						D10	No	*3.7* ↓	Blinded TDM		
						D12	No	*4.0* ↓	Blinded TDM		
						D14	No	*5.3* ↓	Blinded TDM		
						D16	No	*3.4* ↓	Blinded TDM		
						D18	No	*4.2* ↓	Blinded TDM		

						D20	No	*2.9* ↓	Blinded TDM		
24	M	35	#46	Pneumonia (*S. aureus, H. influenzae)*	amox-clav.	D2	No	*1.2* ↓	Blinded TDM	0.25 / -	0.312 / -
						D4	No	*0.7* ↓	Blinded TDM		
51	M	27	#47	Pneumonia (*H. influenzae*)	ceftriaxone	D1	Yes	**14.0**	Blinded TDM	< 0.016	< 0.16
						D2	Yes	**11.3**	Blinded TDM		
						D4	Yes	**15.0**	Blinded TDM		
						D6	Yes	**62.6**	Blinded TDM		
24	M	14	#48	Pneumonia (*H. influenzae, S. aureus*)	ceftriaxone	D2	No	*6.0* ↓	Blinded TDM	0.016 / -	0.16 / -
						D4	No	*4.1* ↓	Blinded TDM		
57	M	12	#49	Burn wound (*S. aureus, P. aeruginosa*)	pip-tazo	D2	No	*2.1 / 0.3* ↓	Blinded TDM	- / 0.03	- / 0.046
						D4	No	*2.0 / 0.3* ↓	Blinded TDM		
53	F	12	#50	Urinary tract (*P. mirabilis, E. faecalis*)	amox-clav.	D2	No	*3.7* ↓	Blinded TDM	/	/
						D4	No	*5.2* ↓	Blinded TDM		
						D6	No	*4.6* ↓	Blinded TDM		
42	F	8	#51	Pneumonia (*S. pneumoniae, S.aureus*)	amox-clav.	D2	Yes	*1.1* ↓	Blinded TDM	0.015 / 2.0	0.019 / 2.5
						D4	Yes	**2.7**	Blinded TDM		
						D6	Yes	*1.5* ↓	Blinded TDM		
						D8	Yes	*1.3* ↓	Blinded TDM		
83	M	18	#52	Pneumonia (*P. mirabilis, E.coli*)	meropenem	D3	Yes	**2.1**	Blinded TDM	0.06 / 0.015	0.06 / 0.015
						D4	Yes	*42.7* ↑	Blinded TDM		
						D6	Yes	**2.2**	Blinded TDM		
			#53	Pneumonia (non identified microorganism)	pip-tazo	D1	No	*38.4 / 6.7* ↑	Blinded TDM	/	/
						D2	No	*51.2 / 10.3* ↑	Blinded TDM		
						D4	No	*49.6 / 3.5* ↑	Blinded TDM		
						D6	No	*/*	Blinded TDM		
						D8	No	*39.5 / 9.1* ↑	Blinded TDM		
						D10	No	**20.1 / 7.3**	Blinded TDM		
			#54	Pneumonia (non identified microorganism)	meropenem	D2	No	**3.9**	Blinded TDM	/	/
						D4	No	**2.4**	Blinded TDM		
25	M	70	#55	Urinary tract (*E. faecalis*)	amoxicillin	D2	Yes	**2.2**	Blinded TDM	0.5	0.625
						D4	Yes	**0.6**	Blinded TDM		
						D6	Yes	**1.8**	Blinded TDM		
			#56, #57	Burn wound and VAP (*P. mirabilis, S. marcesens*)	meropenem	D2	Yes	**1.0**	Blinded TDM	0.03 / 0.06	0.03 / 0.06
					ertapenem	D2	Yes	*0.1* ↓	Blinded TDM	0.006 /	0.06 / 0.32

										0.032	
						D4	Yes	*0.1* ↓	AB switch [f]		
					meropenem	D1	Yes	**1.0**	No [f]	0.03 / 0.06	0.03 / 0.06
						D2	Yes	**0.6**	Blinded TDM		
						D3	Yes	**0.2**	Blinded TDM		
						D4	Yes	**0.5**	Blinded TDM		
						D6	Yes	**0.4**	Blinded TDM		
			#58	Pneumonia (*P. mirabilis*)	meropenem	D1	No	*11.7* ↑	Blinded TDM	/	/
						D2	No	*1.3* ↓	Blinded TDM		
					ceftriaxone	D3	Yes	**7.5**	Blinded TDM	0.19	1.9
						D5	Yes	**8.0**	Blinded TDM		
						D6	Yes	**5.9**	Blinded TDM		
93 †	M	22	#59	Pneumonia (*S. aureus*)	amox-clav.	D2	Yes	**16.9**	Blinded TDM	2.0	2.5
						D4	Yes	**17.3**	Blinded TDM		
71	M	18	#60	Burn wound (*E. coli, E. cloacae, S. aureus, P. vulgaris*)	meropenem	D2	Yes	**1.2**	Blinded TDM	0.015 / 0.015 / 0.12 / 0.06	0.015 / 0.015 / 0.12 / 0.06
17	M	64	#61, #62	Burn wound *(E. faecalis)* and peritonitis	pip-tazo	D2	No	**20.3 / 2.4**	Blinded TDM	1.5 / -	2.31 / -
						D4	No	**17.8 / 2.1**	Blinded TDM		
						D6	No	**14.6 / 2.2**	No [f]		
						D8	No	**12.9 / 2.2**	Blinded TDM		
						D10	No	**8.6 / 1.9**	No [f]		
			#63	Pneumonia (*K. oxytoca*)	meropenem	D1	Yes	**1.3**	Blinded TDM	0.03	0.03
						D2	Yes	**1.7**	Blinded TDM		
						D4	Yes	*15.4* ↑	Blinded TDM		
						D6	Yes	**3.1**	Blinded TDM		
						D8	Yes	**2.2**	Blinded TDM		
			#64	Sepsis (non identified microorganism)	meropenem	D2	No	*0.5* ↓	Blinded TDM	/	/
						D3	No	*0.5* ↓	Blinded TDM		
						D4	No	*0.3* ↓	Blinded TDM		
						D6	No	*0.4* ↓	Blinded TDM		
			#65	Pneumonia (*K. oxytoca*)	meropenem	D1	Yes	**0.7**	Blinded TDM	0.03	0.03
					ceftriaxone	D2	Yes	**23.5**	Blinded TDM	0.047	0.47
						D4	Yes	**39.4**	Blinded TDM		

16	M	55	#66	Bacteriema (*Bacillus spp., G. adiacens*)	imipenem	D2	Yes	*1.4 / 0.8* ^{g} ↓	Blinded TDM	0.12 / > 32	0.15 / > 40
						D4	Yes	*1.6 / 1.0* ^{g} ↓	Blinded TDM		
						D6	Yes	*1.9 / 0.9* ^{g} ↓	Blinded TDM		
						D8	Yes	*2.5 / 1.5* ^{g} ↓	Blinded TDM		
					amox-clav.	D2	Yes	/	/	1.0 / 1.0	1.25 / 1.25
						D3	Yes	*0.7* ↓	Blinded TDM		
						D4	Yes	*0.9* ↓	Blinded TDM		
			#67	Pneumonia (*E. coli*)	pip-tazo	D1	Yes	**1.9 / 0.3**	Blinded TDM	0.5	0.77
						D2	Yes	**3.9 / 0.7**	Blinded TDM		
						D4	Yes	*0.5 / 0.1* ↓	Blinded TDM		
						D6	Yes	**1.0 / 0.2**	Blinded TDM		
50	M	15	#68	Pneumonia (*S. pneumoniae*)	amox-clav.	D2	Yes	**0.4**	Blinded TDM	0.015	0.019
92	F	11	#69	Post grafting antibiotic	amox-clav.	D2	No	**9.6**	Blinded TDM	/	/
						D4	No	**15.2**	Blinded TDM		
			#70	Burn wound (*P. aeuruginosa*)	pip-tazo	D3	Yes	**12.9 / 3.5**	Blinded TDM	2.0	3.08
						D4	Yes	**12.7 / 3.4**	Blinded TDM		
						D6	Yes	*39.8 / 8.8* ↑	Blinded TDM		
62	F	36	#71	Pneumonia (*E. coli*)	pip-tazo	D1	Yes	**3.4 / 0.7**	Blinded TDM	0.75	1.16
						D3	Yes	**1.7 / 0.4**	Blinded TDM		
						D4	Yes	**7.0 / 1.3**	Blinded TDM		
						D6	Yes	**15.2 / 1.9**	Blinded TDM		
						D8	Yes	**14.0 / 1.9**	Blinded TDM		
						D10	Yes	**17.1 / 2.5**	Blinded TDM		
					ceftriaxone	D2	No	*7.5* ↓	Blinded TDM	/	/
83 †	F	35	#72	Pneumonia (*Pantoea spp.*)	amox-clav.	D2	Yes	**12.6**	Blinded TDM	2.0	2.5
						D4	Yes	**7.7**	Blinded TDM		
					ceftriaxone	D2	Yes	**28.0**	Blinded TDM	0.03	0.3
			#73	Post grafting antibiotic	amox-clav.	D2	No	**11.7**	Blinded TDM	/	/
						D4	No	**13.5**	Blinded TDM		
						D6	No	**11.4**	Blinded TDM		

F: Female; **I** : Intervention group; **M**: Male; **S**: Standard-of- care group; **SAPS II**: Simplified acute physiology score II; **TBSA**: Total Body Surface Area.

* Since start of antibiotherapy

** At the time of trough level interpretation

*** According to protein binding (see Suppl. Table 2 for more details)

† Death

Black and bold : appropriate trough level

Black and italic : not in the target trough level

↑ Too high trough level

↓ Too low trough level

[a] Neurotoxicity suspected

[b] The TDM consultant took into account only one MIC

[c] The TDM consultant did not take into account the available MIC

[d] The TDM consultant did not take into account the protein binding

[e] Change on the antibiogram (> 8 mg/L if no MIC)

[f] Rescue TDM (unblinded trough level)

[g] Inappropriate antibiotic (*G. adiacens* MIC > 32 mg/L)

Table 3: Infections characteristics and antibiotic levels results

Infections characteristics and antibiotic levels results	**All patients**	**Patients with unblinded TDM** (Intervention group)	**Patients with blinded TDM** (Standard-of-care group)
Infection types	73	40	33
Pneumonia	42 (57.5)	22 (55.0)	20 (60.6)
Burn wound infection	16 (21.9)	9 (22.5)	7 (21.2)
Sepsis of unknown origin	4 (5.5)	3 (7.5)	1 (3.0)
Urinary tract infections	3 (4.1)	1 (2.5)	2 (6.1)
Catheter related infection	2 (2.7)	1 (2.5)	1 (3.0)
Peritonitis	2 (2.7)	1 (2.5)	1 (3.0)
Post-grafting antibiotics	2 (2.7)	2 (5.0)	0
Others	2 (2.7)	1 (2.5)	1 (3.0)
Infection outcomes (n)	67*	36	31
Resolved (n, %)	63 (94.0)	33 (91.7)	30 (96.8)
Unresolved (n, %)	4 (6.0)	3 (8.3)	1 (3.2)
Number of antibiotic levels	244	118	126
Total number of appropriate antibiotic levels (n) Number	151/244 (61.9)	79/118 (66.9)	72/126 (57.1)
of appropriate first antibiotic levels (n, %) Number of	46/82 (56.1)	22/41 (53.7)	24/41 (58.5)
appropriate subsequent antibiotic levels (n, %)	105/162 (64.8)	57/77 (74.0)	48/85 (56.5)
Not appropriate antibiotic levels (n)	92/244 (37.7)	38/118 (32.3)	54/126 (42.9)
Below the predefined target (n, %)	69/244 (28.3)	25/118 (21.2)	44/126 (34.9)
Over the predefined target (n, %)	23/244 (9.4)	13/118 (11.0)	10/126 (7.9)
Analysis per TBSA	82	41	41
In the target antibiotic levels (n, %)	105	70	35
< 20%	29	20 (69.0)	9 (31.0)
20-40 %	35	23 (65.7)	12 (34.3)
> 40%	41	14 (34.1)	27 (65.9)
Out of the target antibiotic levels	57	20	37
< 20%	16	5 (31.2)	11 (68.8)
20-40 %	18	10 (55.6)	8 (44.4)
> 40%	23	5 (21.7)	18 (78.3)

Number of cures (n) / Defined daily doses of antibiotics (n)	82	1468.8	41	731.1	41	737.7
Amoxicillin (n, %)	22 (25.6)	726.7 (49.5)	10 (24.4)	383.1 (52.4)	12 (29.3)	343.6 (46.6)
Meropenem (n, %)	27 (32.9)	411.8 (28.0)	14 (34.2)	239.3 (32.7)	13 (31.7)	172.5 (23.4)
Flucloxacillin (n, %)	2 (2.4)	121 (8.2)	1 (2.4)	17 (2.3)	1 (2.4)	104 (14.1)
Piperacillin-tazobactam (n, %)	12 (14.6)	88.2 (6.0)	6 (14.6)	33.9 (4.6)	6 (14.6)	54.3 (7.4)
Ceftriaxone (n, %)	12 (14.6)	61 (4.2)	6 (14.6)	28.5 (3.9)	6 (14.6)	32.5 (4.4)
Imipenem-cilastatin (n, %)	2 (2.4)	17.1 (1.2)	1 (2.4)	5.8 (0.8)	1 (2.4)	11.3 (1.5)
Ceftazidime (n, %)	2 (2.4)	17 (1.2)	1 (2.4)	3.5 (0.5)	1 (2.4)	13.5 (1.8)
Ertapenem (n, %)	2 (2.4)	11 (0.7)	1 (2.4)	5 (0.7)	1 (2.4)	6 (0.8)
Cefazoline (n, %)	1 (1.2)	15 (1.0)	1 (2.4)	15 (2.1)	0	0.0
Appropriate antibiotic levels for the most used antibiotics						
Meropenem (n, %)	43/63 (68.3)		28/36 (77.8)		15/27 (55.6)	
Amoxicillin (n, %)	23/35 (65.7)		12/18 (66.7)		11/17 (64.79	
Piperacillin-tazobactam (n, %)	17/28 (60.7)		4/9 (44.4)		13/19 (68.4)	
Ceftriaxone (n, %)	10/11 (90.9)		4/4 (100.0)		6/7 (85.7)	

* =73 - (4 concomitant sites of infection + 2 post-grafting antibiotics)